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(11) Publication number:

0 604 657 A1

(12)

EUROPEAN PATENT APPLICATION
published in accordance with Art.
158(3) EPC

(21) Application number: 93910361.0

(51) Int. Cl. 5: C07F 9/6561, A61K 31/675

(22) Date of filing: 20.05.93

(66) International application number:
PCT/JP93/00660

(67) International publication number:
WO 93/23409 (25.11.93 93/28)

(30) Priority: 21.05.92 JP 128711/92

(43) Date of publication of application:
06.07.94 Bulletin 94/27

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU MC
NL PT SE

(71) Applicant: OTSUKA PHARMACEUTICAL
FACTORY, INC.
115, Aza Kuguhara
Tateiwa
Muya-cho
Naruto-shi Tokushima 772(JP)

(72) Inventor: MIYATA, Kazuyoshi, Raitobiru 302
58-1, Aza Hamabataminami
Salta
Muya-cho, Naruto-shi Tokushima 772(JP)
Inventor: SHOJI, Yasuo, Shinselbiru 302
20-2, Aza Ebisu Maehigashi
Minamihama
Muya-cho, Naruto-shi Tokushima 772(JP)
Inventor: TSUDA, Yoshihiko 127, Aza
Maehama

Kokujima

Muya-cho, Naruto-shi Tokushima 772(JP)
Inventor: TSUTSUMI, Kazuhiko 428-7, Tenjin
Kamisuketou-cho

Tokushima-shi Tokushima 770(JP)

Inventor: INOUE, Yasuhide 35, Aza
Sannokoshi
Yagura

Ohtsu-cho, Naruto-shi Tokushima 770(JP)
Inventor: NABA, Chieko 4-4, Aza Ebisu

Maehigashi

Minamihama

Muya-cho, Naruto-shi Tokushima 772(JP)
Inventor: KUROGI, Yasuhisa Vilasezon 205
189-5, Aza Gomai

Tateiwa

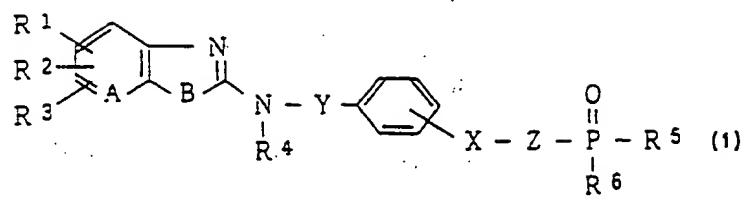
Muya-cho, Naruto-shi Tokushima 772(JP)

(74) Representative: Hansen, Bernd, Dr.rer.nat. et
al
Hoffmann, Eltje & Partner
Patentanwälte
Postfach 81 04 20
D-81904 München (DE)

(54) PHOSPHONIC DIESTER DERIVATIVE.

(57) A phosphonic diester derivative represented by general formula (1). It has the effect of reducing blood sugar
and lipid levels, and so forth, and is useful for treating diabetes, hyperlipidemia, and the like.

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TECHNICAL FIELD

The present invention relates to novel phosphonic diester derivatives.

5 PRIOR ART

The phosphonic diester derivatives of the invention are novel compounds not heretofore described in the literature.

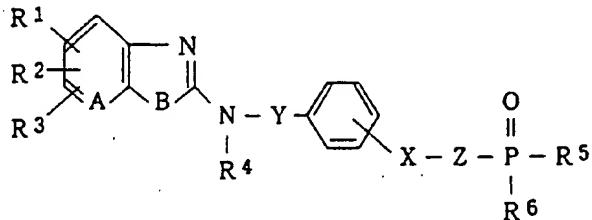
10 DISCLOSURE OF THE INVENTION

The object of the invention is to provide compounds of value as medicines as will be described hereinafter.

The present invention provides a phosphonic diester derivative of the following general formula (1):

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25

[wherein R¹, R² and R³ are the same or different and each represents a hydrogen atom, a lower alkyl group, a phenyl group, a lower alkoxy group, a halogen-substituted lower alkyl group, a halogen-substituted lower alkoxy group, a lower alkanoyl group, a benzoyl group, a (lower)alkoxycarbonyl group, a nitro group, a halogen atom, a (lower)alkylthio group, a phenyl(lower)alkoxy group, a carbamoyl group or a (lower)-alkoxycarbonyl(lower)alkoxy group; R⁴ represents a hydrogen atom, a lower alkyl group or a phenyl(lower)alkyl group; R⁵ and R⁶ are the same or different and each represents a lower alkoxy group, a phenyl group, a phenoxy group, a phenyl(lower)alkoxy group or a hydroxyl group; A represents a carbon atom or a nitrogen atom; B represents a group of the formula =NR⁷ (where R⁷ represents a hydrogen atom, a lower alkyl group or a phenyl(lower)alkyl group), an oxygen atom or a sulfur atom; Y represents a group of the formula C=O or a group of SO₂; X represents an oxygen atom or a bond; Z represents a lower alkylene group optionally having a lower alkyl or phenyl(lower)alkyl group as a substituent or a bond; provided, however, that X and Z do not concurrently represent bonds]

Each of the groups relevant to the above general formula (1) includes the following exemplary species.

40 The lower alkyl group includes straight- or branched-chain lower alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl and so on.

The lower alkoxy group includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentyloxy, hexyloxy and so on.

45 The halogen-substituted lower alkyl group includes trifluoromethyl, pentafluoroethyl, heptafluoropropyl, nonafluorobutyl, undecafluoropentyl, tridecafluorohexyl and so on.

The halogen-substituted lower alkoxy group includes trifluoromethoxy, pentafluoroethoxy, heptafluoropropoxy, nonafluorobutoxy, undecafluoropentyloxy, tridecafluorohexyloxy and so on.

The lower alkanoyl group includes acetyl, propionyl, butyryl, valeryl, pivaloyl, hexanoyl, heptanoyl and so on.

50 The lower alkoxycarbonyl group includes methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl and so on.

The phenyl(lower)alkyl group includes benzyl, 2-phenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, 6-phenylhexyl and so on.

The halogen atom includes fluorine, chlorine, bromine and iodine.

55 The lower alkylthio group includes methylthio, ethylthio, propylthio, butylthio, pentylthio, hexylthio and so on.

The phenyl(lower)alkoxy group includes benzyloxy, 2-phenylethoxy, 3-phenylpropoxy, 4-phenylbutoxy, 5-phenylpentyoxy, 6-phenylhexyloxy and so on.

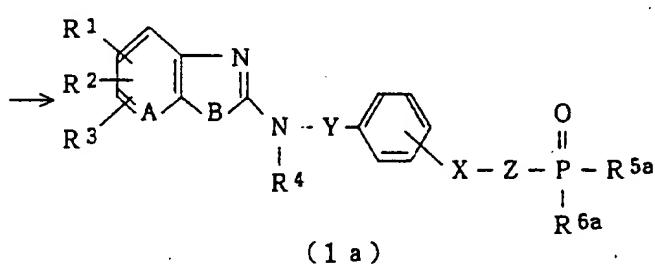
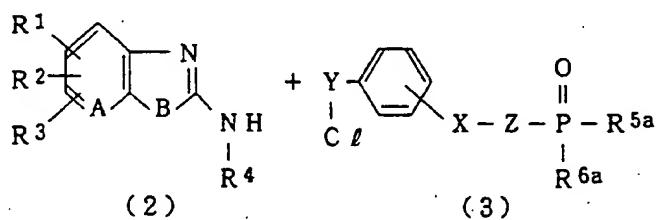
The lower alkoxycarbonyl(lower)alkoxy group includes methoxycarbonylmethoxy, 2-ethoxycarbonylethoxy, 3-ethoxycarbonylpropoxy, 4-ethoxycarbonylbutoxy, 5-ethoxycarbonylpentyloxy, 6-ethoxycarbonyhexyloxy, 2-butoxycarbonylethoxy, hexyloxycarbonylmethoxy and so on.

The lower alkylene group optionally having a lower alkyl or phenyl(lower)alkyl group as a substituent includes methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, ethyldiene, propylidene, butylidene, pentylidene, hexylidene, heptylidene, 2-phenylethyldene, 3-phenylpropylidene, 4-phenylbutylidene, 5-phenylpentylidene, 6-phenylhexylidene, 7-phenylheptylidene and so on.

The phosphonic diester derivative of general formula (1) according to the present invention has excellent hypolipidemic and hypoglycemic activities and is, therefore, useful for the treatment and prevention of various types of hyperlipidemic diseases such as hypercholesterolemia, hypertriglyceridemia, hyperphospholipidemia, hyper-free fatty acidemia, etc. and diabetes. Moreover, the phosphonic diester derivative of the invention not only produces therapeutic and prophylactic effects on cataract but has hypotensive activity as well and is, therefore, of value as a therapeutic and prophylactic agent for cataract and hypertension.

15 The phosphonic diester derivative of general formula (1) according to the invention can be produced by several different processes. Some exemplary processes are schematically shown hereunder.

(Reaction Schema-1)

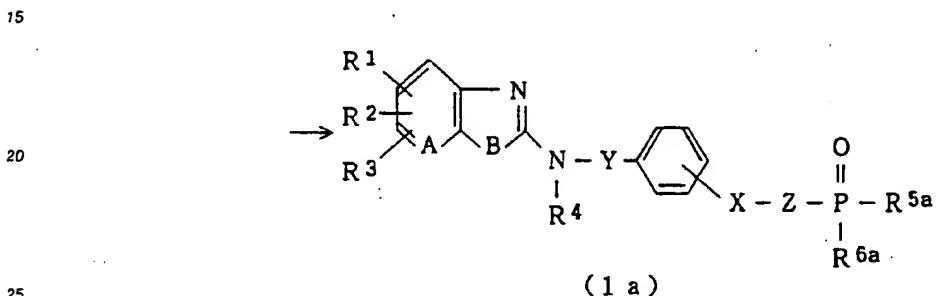
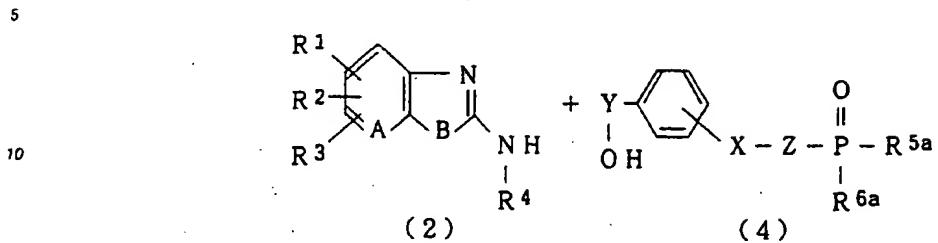


[wherein R¹, R², R³, R⁴, A, B, X, Y and Z are as defined hereinbefore. R^{5a} and R^{6a} are the same or different and each represents a lower alkoxy group, a phenyl group, a phenyl(lower)alkoxy group or a phenoxy group]

According to the process shown in Reaction Schema-1, the objective compound (1a) of the invention can be obtained by reacting compound (2) with acid chloride derivative (3) in the presence of an acid acceptor in an inert solvent. The inert solvent mentioned above includes, among others, aromatic or aliphatic hydrocarbons such as benzene, toluene, xylene, petroleum ether, etc., acyclic or cyclic ethers such as diethyl ether, 1,2-dimethoxyethane, tetrahydrofuran (THF), 1,4-dioxane, etc., ketones such as acetone, methyl ethyl ketone, acetophenone, etc., and halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and so on. The acid acceptor is preferably a tertiary amine such as triethylamine, N,N-diethylaniline, N-methylmorpholine, pyridine, 4-dimethylaminopyridine and so on. The relative amount of said compound (2) and acid chloride derivative (3) is not particularly critical but the latter is preferably used in an equimolar to excess proportion with respect to the former. Usually, the acid acceptor mentioned above is preferably used in an equimolar or excess proportion relative to said acid chloride derivative (3). This reaction proceeds under cooling, at room temperature or under heating but it is usually advantageous to conduct the reaction within the temperature range of 0°C to the reflux temperature

of the solvent used. Generally the reaction goes to completion in about 0.5 - 10 hours.

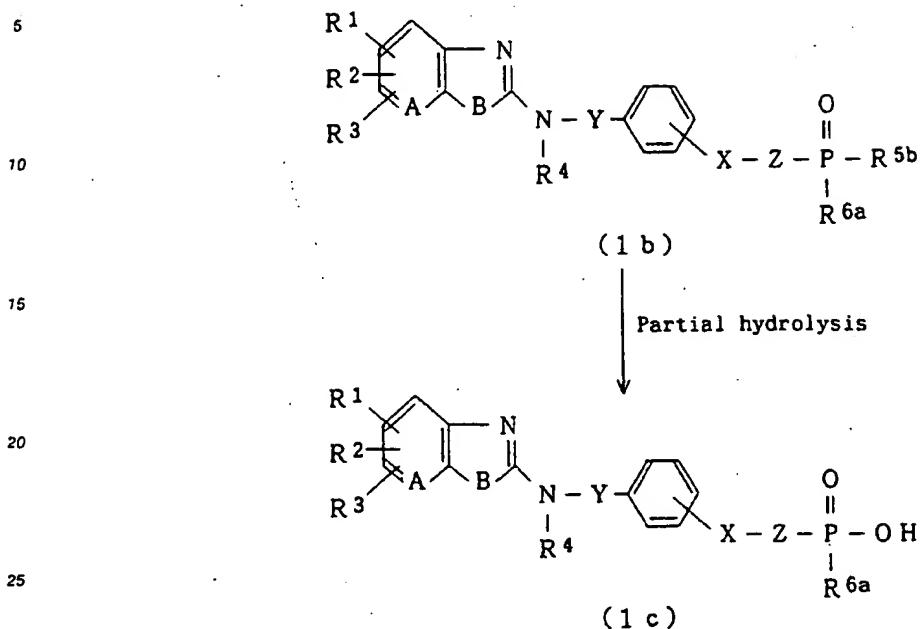
(Reaction Schema-2)



[wherein R¹, R², R³, R⁴, R^{5a}, R^{6a}, A, B, X, Y, and Z are as defined hereinbefore]

According to the process shown in Reaction Schema-2, the objective compound (1a) of the invention can be obtained by reacting compound (2) with compound (4) in the presence of a condensing agent in an inert solvent. The inert solvent which can be used is any of the known aprotic solvents, although N,N-dimethylformamide (DMF) is particularly useful. The condensing agent includes, among others, N,N'-dicyclohexylcarbodiimide (DCC), 1-hydroxybenzotriazole, N-hydroxysuccinimide, diethyl cyanophosphonate, diphenylphosphoryl azide and so on. It is particularly advantageous to employ diethyl cyanophosphonate in combination with triethylamine. The relative amount of compounds (2) and (4) in the above reaction is not critical but can be liberally selected from a broad range. However, it is generally recommendable to use the former compound in an equimolar or excess proportion, preferably an approximately equimolar proportion, relative to the latter compound. The above condensing agent is used in an equimolar to excess proportion, preferably a small excess, relative to compound (4). This reaction is conducted generally under ice-cooling to room temperature for about 0.5 - 2 hours.

(Reaction Schema-3)



[wherein R₁, R₂, R₃, R₄, R^{6a}, A, B, Y and Z are as defined above. R^{5b} represents a lower alkoxy group]

30 The partial hydrolysis shown in the above Reaction Schema-3 is carried out by reacting compound (1b) with a lithium halide such as lithium bromide, lithium chloride, lithium iodide, etc. and thereafter treating the reaction product with a mineral acid such as hydrochloric acid, sulfuric acid and so on. The above reaction can be carried out in an inert solvent, such as acetonitrile, DMF, etc., using a stoichiometric excess of the lithium halide at room temperature ~ the reflux temperature of the solvent for 5 - 24 hours.

35 Among the starting compounds for the production of the compound of the invention, compounds of the formulas (3') and (4') can be prepared by the processes shown below in Reaction Schema-4.

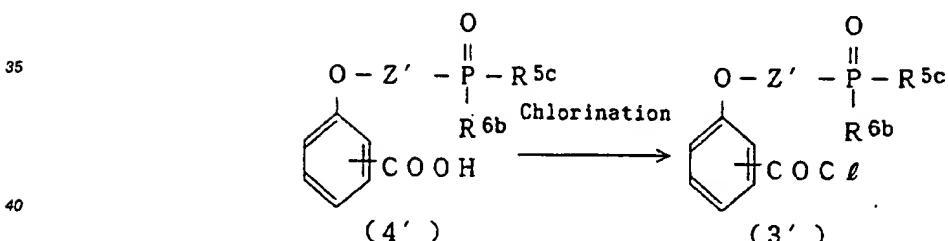
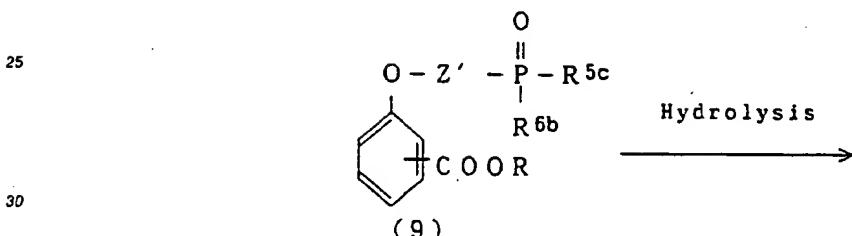
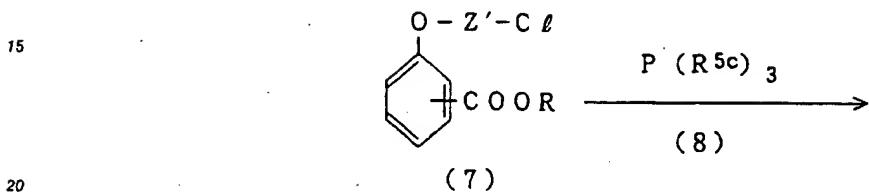
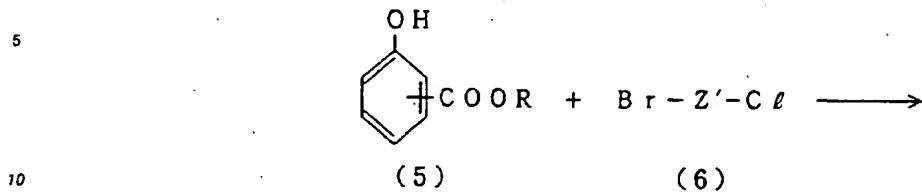
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(Reaction Schema-4)



[wherein R^{5c} represents a lower alkoxy group, a phenoxy group or a phenyl(lower)alkoxy group; R^{6b} is identical to R^{5c}; Z' represents a lower alkylene group; R represents a lower alkyl group]

Referring to the above schema, the reaction between compound (5) and compound (6) is carried out in the presence of an alkali, such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate, sodium hydroxide, etc., in an inert solvent, such as DMF, N,N-dimethylacetamide (DMA), hexamethylphosphoric triamide (HMPA), acetone, methanol, ethanol, methanol-water, ethanol-water and so on. This reaction goes to completion in about 5 - 30 hours at room temperature to the reflux temperature of the solvent.

The resultant compound (7) can be reacted with a phosphorous triester (8) to give compound (9). This reaction can be carried out in a solvent such as lower alcohols, aromatic or aliphatic hydrocarbons, DMF, etc. but is preferably conducted in the absence of a solvent in most cases. If necessary, a salt of iodine such as sodium iodide, potassium iodide, etc. can be added to the reaction system and usually the reaction is preferably conducted using said phosphorous triester (8) in excess at a temperature of about 130 - 170 °C for about 1 - 20 hours.

The compound (9) can then be hydrolyzed to compound (4'). This hydrolysis reaction is carried out in the presence of an aqueous alkali solution, such as aqueous sodium hydroxide solution, aqueous potassium hydroxide solution, etc., in an inert solvent such as methanol, ethanol, 2-propanol, etc. and this reaction goes to completion in about 1 - 15 hours at a temperature somewhere between 0 °C and room temperature.

5 The compound (4') can be chlorinated at the carboxyl function to give compound (5'). This chlorination reaction is carried out using dichloromethane, chloroform, DMF or the like either singly or in combination as the solvent and a small excess of thionyl chloride, phosphorus oxychloride, phosphorus pentachloride or the like as the chlorinating agent at room temperature to about 60 °C for about 1 - 8 hours.

10 The product compound in each of the above processes can be easily isolated and purified by the conventional separation procedures. Such procedures include adsorption chromatography, preparative thin-layer chromatography, solvent extraction, recrystallization and so on.

15 Among the species of compound (I) according to the invention, the compound in which Z is a lower alkylene group having a lower alkyl or phenyl(lower)alkyl group as a substituent may exist as optical isomers which, of course, are subsumed in the concept of the compound of the invention. The above optical isomers can be easily fractionated by the conventional resolution procedures such as optical resolution.

The compound of the invention is put to use in a variety of pharmaceutical compositions prepared using suitable pharmaceutically acceptable carriers. Such pharmaceutically acceptable carriers include various diluents or excipients such as fillers, volume builders, binders, humectants, disintegrators, surfactants, lubricants, etc. and are selectively employed according to the desired dosage form.

20 The above pharmaceutical composition can be provided in a variety of unit dosage forms according to the intended medical treatment. Typical examples are tablets, pills, powders, solutions, suspensions, emulsions, granules, capsules, suppositories, injections (solutions, suspensions, etc.) and eye-drops.

25 The molding of tablets can be made using, as said pharmaceutically acceptable carriers, an excipient such as lactose, sucrose, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, silicic acid, potassium phosphate, etc., a binder such as water, ethanol, propanol, simple syrup, glucose syrup, starch solution, gelatin solution, carboxymethylcellulose, hydroxypropylcellulose, methylcellulose, polyvinylpyrrolidone, etc., a disintegrator such as carboxymethylcellulose sodium, carboxymethylcellulose calcium, low-substituted hydroxypropylcellulose, dry starch, sodium alginate, agar powder, laminaran powder, sodium hydrogen carbonate, calcium carbonate, etc., a surfactant such as polyoxyethylene sorbitan fatty acid ester, sodium lauryl sulfate, stearyl monoglyceride, etc., a disintegration inhibitor such as sucrose, stearin, cacao butter, hydrogenated oil, etc., an absorption promoter such as quaternary ammonium bases, sodium lauryl sulfate, etc., a humectant such as glycerin, starch, etc., an adsorbent such as starch, lactose, kaolin, bentonite, colloidal silica, etc., and a lubricant such as purified talc, salts of stearic acid, boric acid powder, polyethylene glycol and so on. Furthermore, such tablets can be coated, if necessary, to provide sugar-coated tablets, gelatin-coated tablets, enteric tablets, film-coated tablets, etc. or be processed into double-layer or multiple-layer tablets.

In the manufacture of pills, various excipients such as glucose, lactose, starch, cacao butter, hydrogenated vegetable oil, kaolin, talc, etc., binders such as gum arabic powder, gum tragacanth powder, gelatin, ethanol, etc. and disintegrators such as laminaran, starch, etc. can be employed.

40 The capsules can be manufactured in the conventional manner by blending the compound of the invention with any of the various pharmaceutically acceptable carriers mentioned above and filling the resulting composition into hard gelatin capsule shells, soft gelatin capsule shells or the like.

The suppositories can be manufactured using polyethylene glycol, cacao butter, higher alcohols or their esters, gelatin, semisynthetic glycerides, etc. as the carrier.

45 When the compound of the invention is to be provided in an injectable form such as a solution, emulsion or suspension, the preparation is preferably sterilized and rendered isotonic with respect to the blood. As the diluent for use in such a preparation, water, ethyl alcohol, macrogols, propylene glycol, ethoxylated isostearyl alcohol, polyoxy-isostearyl alcohol, polyoxyethylene sorbitan fatty acid esters, etc. can be employed. In this operation, sodium chloride, glucose or glycerin may be added to the composition in a sufficient amount to provide an isotonic solution and the conventional solubilizer, buffer and local anesthetic can also be added.

50 The eye-drops can be manufactured in the conventional manner using sterile distilled water as the vehicle, sodium dihydrogen phosphate and/or sodium monohydrogen phosphate, for instance, as the buffer, sodium chloride or the like as the isotonizing agent, and benzalkonium chloride, chlorobutanol or the like as the antimicrobial agent.

If necessary, various coloring agents, preservatives, perfumes, flavors, sweeteners etc. as well as other pharmacologically active substances can be incorporated in the various dosage forms mentioned above.

There is no particular limitation on the treatment regimen for the pharmaceutical composition of the invention. Thus, the proper regimen can be determined according to the particular dosage form, patient's age, sex and other characteristics, severity of disease and other conditions. For example, said tablets, pills, solutions, suspensions, emulsions, granules and capsules are administered by the oral route. The injections 5 are administered either as they are or in admixture with the conventional glucose, amino acid or other infusions by the intravenous route or, if necessary, alone by the intramuscular, intradermal, subcutaneous or intraperitoneal route. The suppositories are administered intrarectally and the eye-drops are instilled into the eye.

The proportion of the compound of the invention in the pharmaceutical composition described above is 10 not much critical and can be liberally selected from a broad range. Generally, however, it is advantageous to insure that the compound accounts for about 1 to 70 weight % of the final composition. The dosing amount of the pharmaceutical composition can be selected according to the selected regimen, patient's age, sex and other characteristics, severity of disease and other conditions. Generally, however, the dosage 15 of the compound of the invention as the active ingredient is preferably about 0.5 - 20 mg per kg body weight and this amount can be administered in 1 - 4 divided doses. In the case of an ophthalmic preparation for topical application, the dosage of the active compound is preferably selected from the range of about 0.3 - 2 µg.

BEST MODE FOR PRACTICING THE INVENTION

20 The following production examples for the compound of the invention, formulation examples for pharmaceutical compositions using the compound of the invention and pharmacological test examples are intended to describe the invention in further detail.

25 Example 1

Production of diethyl 4-[(2-benzothiazolyl)carbamoyl] benzylphosphonate

In 30 ml of dry dichloromethane were dissolved 3.0 g of 2-aminobenzothiazole and 10 ml of pyridine 30 and while the resulting solution was stirred under ice-cooling, a solution of 5.8 g 4-[(diethoxyphosphoryl)-methyl]benzoyl chloride in 10 ml dry dichloromethane was slowly added dropwise. The stirring was continued at room temperature for 10 hours, after which the reaction mixture was diluted with 30 ml of 10% aqueous sodium hydrogen carbonate solution and extracted with chloroform. The chloroform layer was washed serially with 30 ml of 10% hydrochloric acid and 30 ml of water and dried over anhydrous sodium 35 sulfate and the solvent was distilled off under reduced pressure. The residue was subjected to silica gel column chromatography (eluent: chloroform-ethyl acetate = 1:1) and the resulting crude crystals were recrystallized from ethanol to provide 6.8 g of the title compound as colorless crystals. The structure and melting point of the compound thus obtained are shown in Table 1.

40 Example 2 - 26

Various species of the compound of the invention were obtained in the same manner as Example 1. The structures and melting points of these compounds are also shown in Table 1.

45 Example 27 - 45

Various species of the compound of the invention were produced in the same manner as Example 1. The structures and melting points of these compounds are shown in Table 2. As to an oily compound, its $^1\text{H-NMR}$ spectrum and mass spectrum (MS) are also shown in the table.

50 Example 46

Production of ethyl 4-[(4-methoxybenzothiazol-2-yl)-carbamoyl]benzylphosphonate

55 In 50 ml of dry acetonitrile were suspended 5.2 g (12 mM) of the compound obtained in Example 3 and 5.2 g (60 mM) of lithium bromide and the suspension was refluxed for 20 hours. The reaction mixture was then allowed to cool to room temperature and the resultant precipitate was recovered by filtration and washed with three 60 ml portions of acetonitrile. The crystals thus obtained were dissolved in 400 ml of

water and while the solution was stirred at room temperature, 10 ml of concentrated hydrochloric acid was gradually added. The mixture was stirred at room temperature for 30 minutes, at the end of which time the resultant crystals were recovered by filtration and washed with three 300 ml portions of water. The crude crystals thus obtained were suspended in 200 ml of hot methanol and the insolubles were collected by filtration and washed with 50 ml of methanol. The resultant crystals were further suspended in 200 ml of methanol-chloroform (1:1) and the insolubles were recovered by filtration and washed with 50 ml of methanol and 50 ml of chloroform in the order mentioned to provide 1.8 g of the title compound as colorless crystals. The structure and melting point of this compound are shown in Table 2.

10 Example 47

Production of diethyl 2-[4-{(4-methoxybenzothiazol-2-yl)carbamoyl}phenoxy]ethylphosphonate

To 300 ml of acetonitrile were added 16.6 g (0.1 mole) of ethyl 4-hydroxybenzoate, 31.6 g (0.22 mole) of 1-bromo-2-chloroethane and 60.8 g of anhydrous potassium carbonate and the mixture was refluxed for 20 hours. The reaction mixture was then allowed to cool to room temperature and the solid matter was filtered off. The filtrate was concentrated under reduced pressure. To the resultant oily residue were added 15 g (0.1 mole) of sodium iodide and 50 g (0.3 mole) of triethyl phosphite and the mixture was stirred at 160°C for 18 hours. The reaction mixture was then allowed to cool to room temperature, after which 50 ml of ethanol was added to the reaction mixture. While this mixture was stirred under ice-cooling, 100 ml of 2 N aqueous sodium hydroxide solution was gradually added portionwise. The mixture was stirred at room temperature for 12 hours, at the end of which time 150 ml of water and 150 ml of chloroform were added. After phase separation, the water layer was separated. This aqueous solution was acidified with 150 ml of 4 N hydrochloric acid and extracted with chloroform. The chloroform layer was washed with 200 ml of water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: chloroform-ethyl acetate = 1:1) to provide 3.3 g of 4-[2-(diethoxyphosphoryl)ethoxy]benzoic acid as colorless crystals (m.p. 86-88°C).

Then, 3.0 g (10 mM) of the above crystals were suspended in 15 ml of dry dichloromethane and while the suspension was stirred at room temperature, 1.25 g (10.5 mM) of thionyl chloride and 0.22 g (3 mM) of DMF were added. The mixture was further stirred at 40°C for 1 hour. The resulting reaction mixture was then directly subjected to a reaction similar to that described in Example 1 to provide the title compound.

The structure and melting point of this compound are shown in Table 2.

Example 48

35 Production of diethyl 3-[4-{(4-methoxybenzothiazol-2-yl)carbamoyl}phenoxy]propylphosphonate

Using 1-bromo-3-chloropropane, the procedure of Example 47 was otherwise repeated to provide the title compound via 4-[3-(diethoxyphosphoryl)propoxy]benzoic acid (m.p. 107 - 110°C).

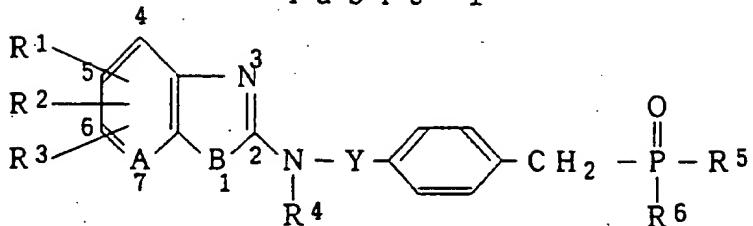
40 The structure and melting point of this compound are shown in Table 2.

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50

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Table 1



OEt: ethoxy group, Me: methyl group,
OMe: methoxy group, Ph: phenyl group

15 Example 1

Structure:

$\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{R}^4 = \text{H}$, $\text{R}^5 = \text{R}^6 = \text{OEt}$, $\text{A} = \text{CH}$, $\text{B} = \text{S}$,
 $\text{Y} = \text{C} = \text{O}$

Mp: 189.5–191°C Recrystallization Solvent: Ethanol

20 Example 2

Structure:

$\text{R}^1 = 4\text{-Me}$, $\text{R}^2 = \text{R}^3 = \text{R}^4 = \text{H}$, $\text{R}^5 = \text{R}^6 = \text{OEt}$,
 $\text{A} = \text{CH}$, $\text{B} = \text{S}$, $\text{Y} = \text{C} = \text{O}$

Mp: 154–156°C

Recrystallization Solvent: Chloroform-n-hexane

25 Example 3

Structure:

$\text{R}^1 = 4\text{-OMe}$, $\text{R}^2 = \text{R}^3 = \text{R}^4 = \text{H}$, $\text{R}^5 = \text{R}^6 = \text{OEt}$,
 $\text{A} = \text{CH}$, $\text{B} = \text{S}$, $\text{Y} = \text{C} = \text{O}$

Mp: 166–168°C Recrystallization Solvent: Ethanol-n-hexane

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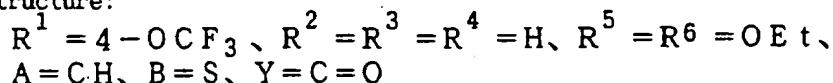
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Example 4

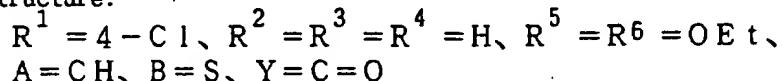
Structure:



Mp: 227-228°C Recrystallization Solvent: Ethanol

Example 5

Structure:

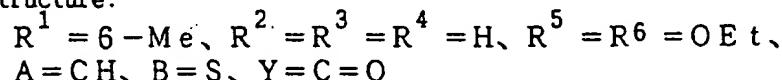


Mp: 183-184.5°C

Recrystallization Solvent: Chloroform-n-hexane

Example 6

Structure:

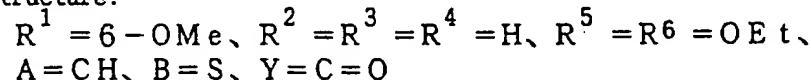


Mp: 210-212°C

Recrystallization Solvent: Chloroform-n-hexane

Example 7

Structure:

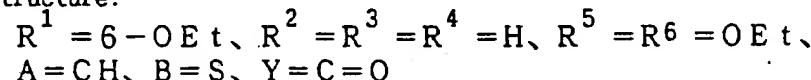


Mp: 175-177°C

Recrystallization Solvent: Chroloform-n-hexane

Example 8

Structure:



Mp: 204.5-206.5°C

Recrystallization Solvent: Chloroform-n-hexane

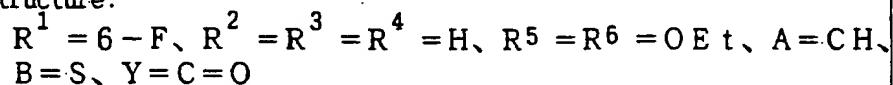
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Example 9

Structure:

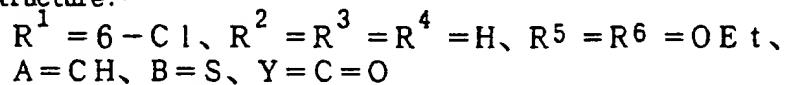


Mp: 210.5 - 212.5°C

Recrystallization Solvent: Chloroform-n-hexane

Example 10

Structure:

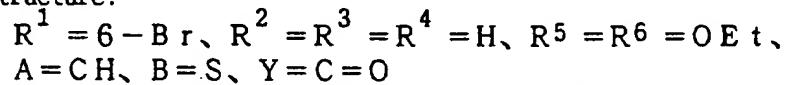


Mp: 227 - 229°C

Recrystallization Solvent: Chloroform-n-hexane

Example 11

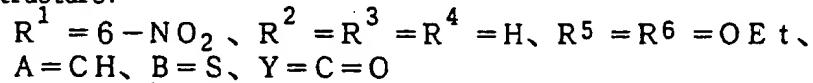
Structure:



Mp: 228 - 229.5°C Recrystallization Solvent: Ethanol-n-hexane

Example 12

Structure:

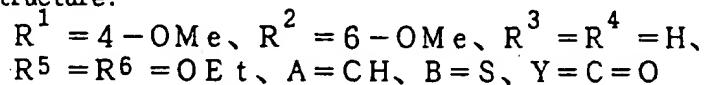


Mp: 249 - 251°C

Recrystallization Solvent: Ethyl acetate-n-hexane

Example 13

Structure:



Mp: 210 - 211°C

Recrystallization Solvent: Dichloromethane-n-hexane

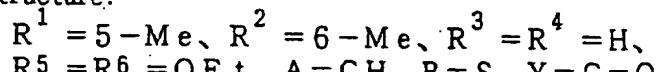
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Example 1 4

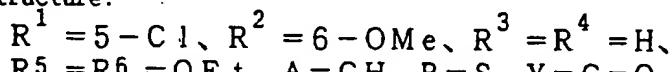
Structure:



Mp: 219–221°C Recrystallization Solvent: Ethanol-n-hexane

Example 1 5

Structure:

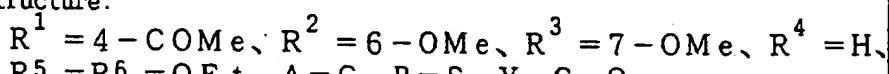


15 Mp: 209–212°C

Recrystallization Solvent: Dichloromethane-n-hexane

Example 1 6

Structure:

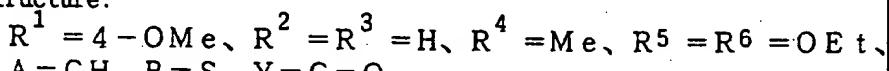


25 Mp: 184–187°C

Recrystallization Solvent: Chloroform-n-hexane

Example 1 7

Structure:

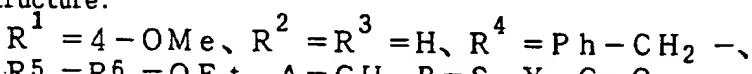


35 Mp: 168–169°C

Recrystallization Solvent: Dichloromethane-n-hexane

Example 1 8

Structure:



45 Mp: 116–119°C

Recrystallization Solvent: Dichloromethane-n-hexane

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Example 19

Structure:

5 $R^1 = 4 - OMe$ 、 $R^2 = R^3 = R^4 = H$ 、 $R^5 = R^6 = OEt$ 、
 A=CH、 B=S、 Y=SO₂

Mp: 200-204°C

Recrystallization Solvent: Dichloromethane-n-hexane

Example 20

Structure:

15 $R^1 = 4 - OMe$ 、 $R^2 = R^3 = R^4 = H$ 、 $R^5 = R^6 = OMe$ 、
 A=CH、 B=S、 Y=C=O

Mp: 162.5-164.5°C

Recrystallization Solvent: Ethyl acetate

Example 21

Structure:

20 $R^1 = R^2 = R^3 = R^4 = H$ 、 $R^5 = R^6 = OEt$ 、
 A=N、 B=S、 Y=C=O

Mp: 206-208°C

Recrystallization Solvent: Methanol-n-hexane

Example 22

Structure:

25 $R^1 = R^2 = R^3 = H$ 、 $R^4 = Me$ 、
 $R^5 = R^6 = OEt$ 、 A=N、 B=S、 Y=C=O

Mp: 133-135°C

Recrystallization Solvent: Dichloromethane-n-hexane

Example 23

Structure:

30 $R^1 = R^2 = R^3 = H$ 、 $R^4 = Ph - CH_2 -$ 、 $R^5 = R^6 = OEt$ 、
 A=N、 B=S、 Y=C=O

Mp: 137-139°C

Recrystallization Solvent: Dichloromethane-n-hexane

45

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Example 2 4

Structure:

5 $R^1 = R^2 = R^3 = R^4 = H$ 、 $R^5 = R^6 = OEt$ 、 $A = CH$ 、
 $B = NH$ 、 $Y = C = O$

Mp: 173.5 - 175.5 °C

Recrystallization Solvent: Ethyl acetate-n-hexane

Example 2 5

Structure:

10 $R^1 = R^2 = R^3 = R^4 = H$ 、 $R^5 = R^6 = OEt$ 、 $A = CH$ 、
 $B = N-Me$ 、 $Y = C = O$

Mp: 188 - 190 °C

Recrystallization Solvent: Ethyl acetate-n-hexane

Example 2 6

Structure:

20 $R^1 = R^2 = R^3 = R^4 = H$ 、 $R^5 = R^6 = OEt$ 、 $A = CH$ 、
 $B = N-CH_2 Ph$ 、 $Y = C = O$

Mp: 112 - 113 °C

Recrystallization Solvent: Ethyl acetate-n-hexane

30

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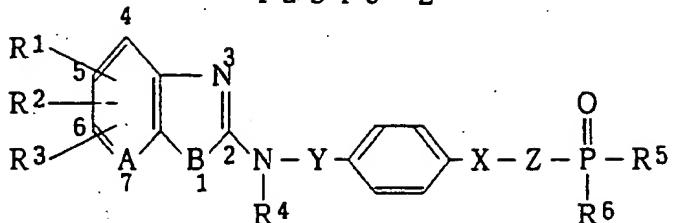
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Table 2



OEt: ethoxy group, Me: methyl group,
OMe: methoxy group, Ph: phenyl group

Example 27

Structure:

R₁ = 4-OMe, R₂ = R₃ = R₄ = H,
R₅ = R₆ = -OCH(CH₃)₂, A = CH, B = S,
Y = C=O, X = Single bond, Z = -CH₂-

Mp: 206.5-207.5°C

Recrystallization Solvent: Ethyl acetate-n-hexane

Example 28

Structure:

R₁ = 4-OMe, R₂ = R₃ = R₄ = H,
R₅ = R₆ = -O-n-C₄H₉, A = CH, B = S, Y = C=O
X = Single bond, Z = -CH₂-

Mp: 167-168.5°C

Recrystallization Solvent: Ethanol-n-hexane

Example 29

Structure:

R₁ = 4-OMe, R₂ = R₃ = R₄ = H, R₅ = OMe,
R₆ = OEt, A = CH, B = S, Y = C=O, X = Single bond,
Z = -CH₂-

Mp: 166-168°C

Recrystallization Solvent: Ethyl acetate-n-hexane

Example 3 0

Structure:

5 $R_1 = 4 - OMe$ 、 $R_2 = R_3 = R_4 = H$ 、 $R_5 = OEt$ 、
 $R_6 = -OCH(CH_3)_2$ 、 $A = CH$ 、 $B = S$ 、 $Y = C = O$ 、
 $X = \text{Single bond}$ 、 $Z = -CH_2 -$

Mp: 155~157°C

Recrystallization Solvent: Ethanol-n-hexane

Example 3 1

Structure:

15 $R_1 = 4 - OMe$ 、 $R_2 = R_3 = R_4 = H$ 、 $R_5 = Ph$ 、
 $R_6 = OEt$ 、 $A = CH$ 、 $B = S$ 、 $Y = C = O$
 $X = \text{Single bond}$ 、 $Z = -CH_2 -$

Mp: 101~104°C

Recrystallization Solvent: Ethyl acetate-n-hexane

Example 3 2

Structure:

25 $R_1 = 6 - CF_3$ 、 $R_2 = R_3 = R_4 = H$ 、 $R_5 = R_6 = OEt$ 、
 $A = CH$ 、 $B = S$ 、 $Y = C = O$ 、 $X = \text{Single bond}$ 、 $Z = -CH_2 -$

Mp: 223~224.5°C

Recrystallization Solvent: Dichloromethane-n-hexane

Example 3 3

Structure:

35 $R_1 = 4 - COPh$ 、 $R_2 = 6 - Cl$ 、 $R_3 = R_4 = H$ 、
 $R_5 = R_6 = OEt$ 、 $A = CH$ 、 $B = S$ 、 $Y = C = O$ 、
 $X = \text{Single bond}$ 、 $Z = -CH_2 -$

Mp: 233~234°C (dec.)

Recrystallization Solvent: Chloroform-n-hexane

40

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Example 3 4**Structure:**

5 $R^1 = 4 - COMe$ 、 $R^2 = 6 - Br$ 、 $R^3 = R^4 = H$ 、

$R^5 = R^6 = OEt$ 、 $A = CH$ 、 $B = S$ 、 $Y = C = O$ 、

$X = \text{Single bond}$ 、 $Z = -CH_2 -$

10 Mp: 219~220°C (dec.)

Recrystallization Solvent: Dichloromethane-n-hexane

Example 3 5**Structure:**

15 $R^1 = 6 - COOEt$ 、 $R^2 = R^3 = R^4 = H$ 、 $R^5 = R^6 = OEt$ 、

$A = CH$ 、 $B = S$ 、 $Y = C = O$ 、 $X = \text{Single bond}$ 、 $Z = -CH_2 -$

Mp: 225~226.5°C

20 Recrystallization Solvent: Chloroform-n-hexane

Example 3 6**Structure:**

25 $R^1 = 6 - SME$ 、 $R^2 = R^3 = R^4 = H$ 、 $R^5 = R^6 = OEt$ 、

$A = CH$ 、 $B = S$ 、 $Y = C = O$ 、 $X = \text{Single bond}$ 、 $Z = -CH_2 -$

Mp: 179~180°C

20 Recrystallization Solvent: Dichloromethane-n-hexane

Example 3 7**Structure:**

30 $R^1 = 6 - OCH_2 Ph$ 、 $R^2 = R^3 = R^4 = H$ 、 $R^5 = R^6 = OEt$ 、

$A = CH$ 、 $B = S$ 、 $Y = C = O$ 、 $X = \text{Single bond}$ 、 $Z = -CH_2 -$

35 Mp: 182~183°C

Recrystallization Solvent: Chloroform-n-hexane

Example 3 8**Structure:**

40 $R^1 = 6 - CONH_2$ 、 $R^2 = R^3 = R^4 = H$ 、 $R^5 = R^6 = OEt$ 、

$A = CH$ 、 $B = S$ 、 $Y = C = O$ 、 $X = \text{Single bond}$ 、 $Z = -CH_2 -$

Mp: 257~258.5°C

45 Recrystallization Solvent: Chloroform-methanol

Example 3 9

Structure:

R₁ = 4 - OMe, R₂ = R₃ = R₄ = H, R₅ = R₆ = OPh,
 A = CH, B = S, Y = C = O, X = O, Z = Single bond

¹H-NMR (δ : ppm) [CDCl₃] :

3. 55 (s, 3H), 6. 73 (d, 1H, J = 7. 9 Hz),
 7. 1 - 7. 5 (m, 12H), 7. 9 - 8. 4 (m, 4H),
 12. 0 (b.r. s, 1H)

MS (EI) m/z :

532 (M⁺), 353 (M - C₈H₇N₂OS, base)

Example 4 0

Structure:

R₁ = 5 - Cl, R₂ = R₃ = R₄ = H, R₅ = R₆ = OEt,
 A = CH, B = O, Y = C = O, X = Single bond, Z = -CH₂ -
 Mp: 190. 5 ~ 192. 0°C

Recrystallization Solvent: Ethyl acetate

Example 4 1

Structure:

R₁ = 6 - OCH₂ - COOEt, R₂ = R₃ = R₄ = H,
 R₅ = R₆ = OEt,
 A = CH, B = S, Y = C = O, X = Single bond, Z = -CH₂ -
 Mp: 187. 5 - 188. 5°C

Recrystallization Solvent: Chloroform-n-hexane

Example 4 2

Structure:

R₁ = 4 - OMe, R₂ = R₃ = R₄ = H, R₅ = R₆ = OEt,
 A = CH, B = S, Y = C = O, X = Single bond, Z = -CH -
 CH₂ Ph
 Mp: 74 - 76°C Recrystallization Solvent: Chloroform-n-hexane

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Example 4 3

Structure:

5 $R^1 = 4 - OMe$ 、 $R^2 = R^3 = R^4 = H$ 、 $R^5 = R^6 = OEt$ 、
 $A = CH$ 、 $B = S$ 、 $Y = C = O$ 、 $X = \text{Single bond}$ 、 $Z = -CH_2 -$
 CH_3

10 Mp: 85~87°C Recrystallization Solvent: Ethanol-n-hexane

Example 4 4

Structure:

15 $R^1 = 4 - Ph$ 、 $R^2 = 6 - Br$ 、 $R^3 = R^4 = H$ 、
 $R^5 = R^6 = OEt$ 、 $A = CH$ 、 $B = S$ 、 $Y = C = O$ 、
 $X = \text{Single bond}$ 、 $Z = -CH_2 -$

20 Mp: 208~209°C Recrystallization Solvent: Chloroform-n-hexane

Example 4 5

Structure:

25 $R^1 = 4 - OMe$ 、 $R^2 = R^3 = R^4 = H$ 、 $R^5 = OEt$ 、
 $R^6 = OCH_2 Ph$ 、 $A = CH$ 、 $B = S$ 、 $Y = C = O$ 、
 $X = \text{Single bond}$ 、 $Z = -CH_2 -$

30 Mp: 140~143°C Recrystallization Solvent: Ethyl acetate-n-hexane

Example 4 6

Structure:

35 $R^1 = 4 - OMe$ 、 $R^2 = R^3 = R^4 = H$ 、 $R^5 = OH$ 、 $R^6 = OEt$ 、
 $A = CH$ 、 $B = S$ 、 $Y = C = O$ 、 $X = \text{Single bond}$ 、 $Z = -CH_2 -$

Mp: 255~256.5°C (dec.)

40

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Example 4 7

Structure:

5 R₁ = 4 - O Me, R₂ = R₃ = R₄ = H, R₅ = R₆ = O Et,

A = CH, B = S, Y = C = O, X = O, Z = -CH₂ CH₂ -

Mp: 150 - 153°C

10 Recrystallization Solvent: Dichloromethane-n-hexane

Example 4 8

Structure:

15 R₁ = 4 - O Me, R₂ = R₃ = R₄ = H, R₅ = R₆ = O Et,

A = CH, B = S, Y = C = O, X = O, Z = -CH₂ CH₂ CH₂ -

Mp: 168 ~ 170. 5°C

20 Recrystallization Solvent: Ethanol-n-hexane

Formulation Example 1

25 Manufacture of tablets using the compound obtained in Example 3 as an active ingredient, tablets (1000 tablets) each containing 250 mg of the active ingredient were manufactured according to the following formula.

Ingredient	Amount (g)
Compound of Example 3	250
Lactose (JP)	33.5
Corn starch (JP)	16.5
Carboxymethylcellulose calcium (JP)	12.5
Methylcellulose (JP)	6.0
Magnesium stearate (JP)	1.5
Total	320.0

40 According to the above formula, the compound of Example 3, lactose, corn starch and carboxymethyl cellulose calcium were well blended and granulated using an aqueous solution of methyl cellulose. The granulation was passed through a 24-mesh sieve and the granules under the sieve were mixed with magnesium stearate and compression-molded.

45 Formulation Example 2 Manufacture of capsules

Using the compound obtained in Example 5 as an active ingredient, hard gelatin capsules (1000 units) each containing 250 mg of the active ingredient were manufactured according to the following formula.

50

55

Ingredient	Amount (g)
Compound of Example 5	250
Crystalline cellulose (JP)	30
Corn starch (JP)	17
Talc (JP)	2
Magnesium stearate (JP)	1
Total	300

5

Thus, according to the above formula, the respective ingredients were finely divided and the powders obtained were blended to give a homogeneous composition. This composition was filled into proper-sized gelatin capsule shells for oral administration to provide the objective capsules.

15 Formulation Example 3 Manufacture of granules

Using the compound obtained in Example 13 as an active ingredient, granules (1000 g) containing 500 mg of the active ingredient in each gram were manufactured according to the following formula.

20

Ingrdient	Amount (g)
Compound of Example 13	500
Crystalline cellulose (JP)	100
Corn starch (JP)	250
Lactose (JP)	100
Carboxymethylcellulose calcium (JP)	40
Hydroxypropylmethylcellulose (JP)	10
Total	1000

25

Thus, according to the above formula, the compound of Example 13, lactose, corn starch, crystalline cellulose and carboxymethylcellulose calcium were thoroughly blended and kneaded with an aqueous solution of hydroxypropylcellulose. The resultant composition was granulated using an extrusion granulator and dried at 50 °C for 2 hours to provide the objective granules.

30

35 Pharmacological Test Example 1

Hypolipidemic effect in rats with Triton WR1339-induced hyperlipidemia

40

An experiment for assaying hypolipidemic activity in rats with Triton WR1339-induced hyperlipidemia was performed according to the method of Kuroda et al. [Biochem. Biophys. Acta., 489, 119 (1977)], as follows.

45

Thus, using 6 - 7-week-old male Wistar rats in groups of 6 (test groups), a solution of 300 mg/kg Triton in physiological saline was administered into the tail vein and, at the same time, 100 mg/kg of the test compound suspended in 5% gum arabic solution was administered orally.

As a control group, a group of 6 rats given Triton were orally dosed with 5% gum arabic solution.

Twenty-four hours after administration of Triton, blood was withdrawn from the abdominal aorta and the plasma total cholesterol and triglyceride were determined using Cholesterol C-Test Wako and Triglyceride G-Test Wako (both available from Wako Pure Chemical Industries, Ltd.), respectively.

50

Using the measured values in the control group as references, the rates of decrease (%) in plasma total cholesterol and triglyceride in the test group were calculated by means of the following equation.

55

$$\text{Rate of decrease (Z)} = \frac{\text{(Control group value)} - \text{(Test group value)}}{\text{(Control group value)}} \times 100$$

The test rats were deprived of food before Triton administration through completion of blood sampling but allowed free access to drinking water. The rates of decrease in total cholesterol are shown in Table 3 and those in triglyceride are shown in Table 4.

5

Table 3

	Test compound (Example No.)	Rate of decrease in total cholesterol (%)
10	1	40
	3	56
	13	70
	26	43
	27	42
15	29	47
	30	79
	31	69
	34	71
20	42	45
	43	45
	45	62

25

Table 4

	Test compound (Example No.)	Rate of decrease in triglyceride (%)
30	1	62
	2	44
	3	83
	4	47
	10	40
35	11	44
	13	94
	20	48
	25	54
	26	63
40	27	81
	29	87
	30	95
	31	92
	32	47
45	34	97
	42	81
	43	80
	45	91

50 It is apparent from Tables 3 and 4 that all species of the compound of the invention have excellent hypolipidemic activity.

Pharmacological Test Example 2

55 Hypoglycemic effect in rats with streptozotocin-induced diabetes

The rat model of streptozotocin-induced diabetes was constructed according to Doi's method [Folia Endocrinologica Japonica, 51 (3), 129 (1975)] as below and the hypoglycemic activity of the compound of

the invention was assayed in the model by the following procedure.

Thus, using 5-week-old male Wistar rats in groups of 7 (test groups), 100 mg/kg of streptozotocin dissolved in 0.01 M citrate buffer (pH 4.5) was administered into the tail vein and on day 6 after this administration, a suspension of 30 mg/kg of the compound obtained in Example 3 in 5% gum arabic solution was orally administered.

As a control group, a group of 6 rats given streptozotocin were orally dosed with 5% gum arabic solution.

Four hours after administration of the test compound or 5% gum arabic solution, blood was withdrawn from the abdominal aorta and the plasma glucose was determined using Glucose C II-Test Wako (Wako Pure Chemical Industries, Ltd.).

The results in terms of mean \pm SD are shown below in Table 5.

Table 5

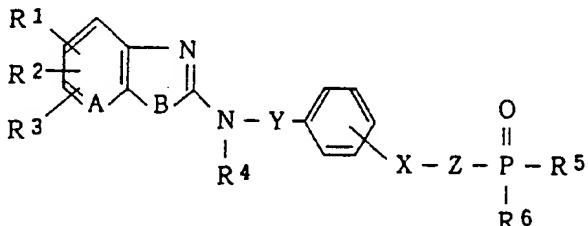
	Plasma glucose level (mg/dl)
Control group	588 \pm 69
Test group	495 \pm 53 **

**: P<0.01 [Dunnet's test]

It is apparent from the above table that the plasma glucose level in the test group was significantly depressed as compared with the control group, indicating that the compound of the invention has excellent hypoglycemic activity.

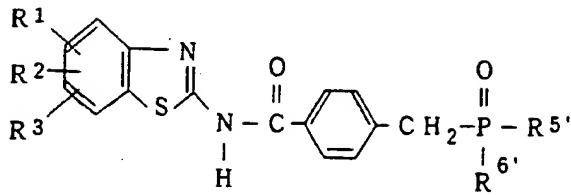
Claims

1. A phosphonic diester derivative of the general formula



[wherein R¹, R² and R³ are the same or different and each represents a hydrogen atom, a lower alkyl group, a phenyl group, a lower alkoxy group, a halogen-substituted lower alkyl group, a halogen-substituted lower alkoxy group, a lower alkanoyl group, a benzoyl group, a (lower)alkoxycarbonyl group, a nitro group, a halogen atom, a (lower)alkylthio group, a phenyl(lower)alkoxy group, a carbamoyl group or a (lower)alkoxycarbonyl(lower)alkoxy group; R⁴ represents a hydrogen atom, a lower alkyl group or a phenyl(lower)alkyl group; R⁵ and R⁶ are the same or different and each represents a lower alkoxy group, a phenyl group, a phenoxy group, a phenyl(lower)alkoxy group or a hydroxyl group; A represents a carbon atom or a nitrogen atom; B represents a group of the formula =NR⁷ (where R⁷ represents a hydrogen atom, a lower alkyl group or a phenyl(lower)alkyl group), an oxygen atom or a sulfur atom; Y represents a group of the formula C=O or a group of SO₂; X represents an oxygen atom or a bond; Z represents a lower alkylene group optionally having a lower alkyl or phenyl(lower)alkyl group as a substituent or a bond; provided, however, that X and Z do not concurrently represent bonds]

2. The phosphonic diester derivative of Claim 1 which is represented by the general formula



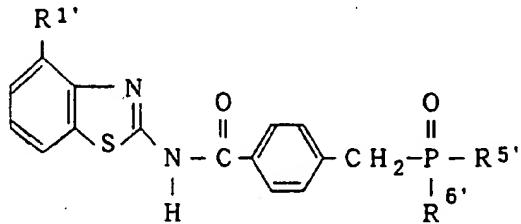
10 [wherein R¹, R² and R³ are the same or different and each represents a hydrogen atom, a lower alkyl group, a phenyl group, a lower alkoxy group, a halogen-substituted lower alkyl group, a halogen-substituted lower alkoxy group, a lower alkanoyl group, a benzoyl group, a (lower)alkoxycarbonyl group, a nitro group, a halogen atom, a (lower)alkylthio group, a phenyl(lower)alkoxy group, a carbamoyl group or a (lower)alkoxycarbonyl(lower)alkoxy group; R^{5'} and R^{6'} are the same or different and each represents a lower alkoxy group, a phenyl group or a phenyl(lower)alkoxy group].

15

3. The phosphonic diester derivative of Claim 2 wherein R¹, R² and R³ are groups selected from the class consisting of a hydrogen atom, a lower alkoxy group, a lower alkanoyl group and a halogen atom.

20

4. The phosphonic diester derivative of Claim 3 which may be represented by the general formula



30 [wherein R^{1'} represents a lower alkoxy group, R^{5'} and R^{6'} are the same or different and each represents a lower alkoxy group, a phenyl group or a phenyl(lower)alkoxy group].

35

5. The phosphonic diester derivative of Claim 3 which is a compound selected from the class consisting of
 - (1) Diethyl 4-[(4-methoxybenzothiazol-2-yl)carbamoyl]benzylphosphonate,
 - (2) Diethyl 4-[(4,6-dimethoxybenzothiazol-2-yl)-carbamoyl]benzylphosphonate,
 - (3) Diethyl 4-[(4-acetyl-6-bromobenzothiazol-2-yl)carbamoyl]benzylphosphonate, and
 - (4) Diethyl 4-[(4-chlorobenzothiazol-2-yl)carbamoyl]benzylphosphonate.

40

6. The phosphonic diester derivative of Claim 5 which is diethyl 4-[(4-methoxybenzothiazol-2-yl)-carbamoyl]benzylphosphonate.

45

7. An antihyperlipidemic composition comprising the phosphonic diester derivative claimed in any of Claims 1 through 6 as an active ingredient.
8. An antidiabetic composition comprising the phosphonic diester derivative claimed in any of Claims 1 through 6 as an active ingredient.

50

9. A method of treating hyperlipidemia characterized by administering to a patient a pharmacologically effective amount of the antihyperlipidemic composition claimed in Claim 7.

55

10. A method of treating diabetes characterized by administering a pharmacologically effective amount of the antidiabetic composition claimed in Claim 8.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP93/00660

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl⁵ C07F9/6561, A61K31/675

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int. Cl⁵ C07F9/6561, A61K31/675

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP, A, 2-500744 (Aktiebolaget Haessle), March 15, 1990 (15. 03. 90), & WO, A, 8803921 & EP, A, 279149 & US, A, 5215974	1-8

Further documents are listed in the continuation of Box C. See patent family annex.

Special categories of cited documents:	
"A"	document defining the general state of the art which is not considered to be of particular relevance
"E"	earlier document but published on or after the international filing date
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O"	document referring to an oral disclosure, use, exhibition or other means
"P"	document published prior to the international filing date but later than the priority date claimed
"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"Z"	document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
September 21, 1993 (21. 09. 93)	October 12, 1993 (12. 10. 93)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP93/00660

Box I. Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 9, 10
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 9 and 10 pertain to methods for treatment of the human body by therapy.

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II. Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.